PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Improvements in or relating to Cyclic Nitrogen Compounds

We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the production of cyclic nitrogen compounds.

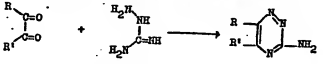
According to the present invention, there are provided novel 3-amino asymmetric (*as*) triazines having the formula

in which R and R^1 may be separate or joined to complete a second ring, each of R and R^1, when separate, representing a hydrogen atom or a hydroxyl or alkyl group, and R and R^1, when joined, representing a polymethylene or substituted polymethylene radical. These triazines are valuable intermediates in the production of other compounds.

These 3-amino-*as*-triazines are produced by reacting aminoguanidine with a 1,2-dicarbonyl compound of the formula

where R and R^1 have the significance previously assigned.

This reaction may be illustrated as follows



in each instance R and R^1 representing substituents as defined above.

Examples of 1,2-dicarbonyl compounds which can be used in this reaction are glyoxal and monoalkyl glyoxals such as methylglyoxal (pyruvic aldehyde), ethylglyoxal, propylglyoxal, isopropylglyoxal, butylglyoxal, isobutylglyoxal, tertiary butylglyoxal, amylglyoxal and hexylglyoxal, 1,2-diketones such as 2,3-butanedione (diacetyl), 2,3-pentanedione, 2,3-hexanedione, 3,4-hexanedione, 3,4-heptanedione, 2,3-octanedione, 3,4-octanedione, 4,5-octanedione, 5,6-decanedione, 2,5-dimethyl-3,4-hexanedione, 5-methyl-3,4-hexanedione, and cyclohexanedione, and α-oxocarboxylic and α-dicarboxylic acids such as pyruvic acid, glyoxalic acid, and oxalic acid.

The reaction is conveniently effected by intimately contacting a 1,2-dicarbonyl with aminoguanidine in the presence of a suitable solvent. Examples of solvents which are particularly useful are water, the lower alcohols such as ethanol and propanol, and dioxane. A single solvent or a mixture of such solvents may be used if desired. In addition, the reaction is conducted at a neutral or basic pH. A neutral or basic pH can be conveniently produced by the use of alkali metal and alkaline earth metal hydroxides, bicarbonates and carbonates. A pH of about 8 to 10 is preferred to obtain the highest yields.

Aminoguanidine may be reacted in the form of a salt or as the free base. However, the reaction is faster when the free base is used. Although aminoguanidine is usually obtained commercially in the form of a salt, the free base may be prepared according to conventional methods. Thus, the free base may be obtained by adding hydrochloric acid to

aminoguanidine bicarbonate followed by the addition of a slight excess of sodium hydroxide.

Room temperatures and elevated temperatures may be used for the reaction although temperatures below 60°C. are preferred. The reaction is exothermic in nature and to prevent overheating the reactants are combined slowly. The reaction is completed within a short time after the reactants are combined. The desired 3-amino-*as*-triazines are substantially insoluble in most solvents and immediately precipitate from the reaction mixture from which the products may be recovered by filtration and purified, if desired, by conventional methods.

When an unsymmetrical 1,2-dicarbonyl such as an alkyl glyoxal, or a 1,2-diketone having dissimilar substituents, is reacted with aminoguanidine, it is not known for certain whether the resulting 3-amino-5,6-substituted-*as*-triazine consists of one product or a mixture of isomeric compounds. Thus, when methylglyoxal is reacted with aminoguanidine it may be that 3-amino-5-methyl-*as*-triazine or 3-amino-6-methyl-*as*-triazine, or a mixture of these isomers, is produced. It is, however, believed that the use of unsymmetrical 1,2-dicarbonyls usually results in a mixture of isomeric 3-amino-5(6)-substituted-*as*-triazines, but to show that a particular substituent may be in either the 5 or 6 position the alternative position is indicated in parenthesis; for example, the reaction product of methylglyoxal and aminoguanidine is designated 3-amino-5(6)-methyl-*as*-triazine.

Examples of some 3-amino-*as*-triazines which can be prepared by reacting the corresponding 1,2-dicarbonyl compound with aminoguanidine are 3-amino-*as*-triazine; 3-amino-5(6)-methyl-*as*-triazine, 3-amino - 5(6)-ethyl-*as*-triazine, 3-amino - 5(6)-propyl-*as*-triazine, 3-amino-5(6)-butyl-*as*-triazine, 3-amino-5(6)-isobutyl-*as*-triazine, 3-amino - 5(6)-amyl-*as*-triazine, 3-amino - 5(6), - hexyl-*as*-triazine, 3-amino - 5,6-dimethyl-*as*-triazine, 3-amino-5,6-diethyl-*as*-triazine, 3-amino-5,6-dipropyl-*as*-triazine, 3-amino - 5,6 - diisopropyl-*as*-triazine, 3-amino-5,6-dibutyl-*as*-triazine, 3-amino-5,6-dihexyl-*as*-triazine, 3-amino - 5(6)-methyl-6(5)-ethyl-*as*-triazine, 3 - amino-5(6)-ethyl - 6(5) - butyl-*as*-triazine, 3-amino-5(6)-methyl-6(5)-propyl-*as*-triazine, 3-amino-5(6)-ethyl-6(5)-hexyl-*as*-triazine, 3-amino-5,6,7,8-tetrahydro - 1,2,4 - benzo-triazine, 3-amino-5-hydroxy-*as*-triazine, 3-amino-5,6-dihydroxy-*as*-triazine, and 3-amino-5-hydroxy-6-methyl-*as*-triazine.

The 3-amino-*as*-triazines are valuable intermediates in the production of other valuable compounds. For example, by reacting *p*-nitrophenylisocyanate with 3-amino-*as*-triazine or 3-amino-*as*-triazines which contain substituents in the 5- and/or 6-positions there is obtained 1-(4-nitrophenyl) -3- (3-*as*-triazinyl) urea or the corresponding 5-6 substituted derivatives. Specific examples of ther compounds which can be prepared in this manner are 1-(4-nitrophenyl)-3-(3 - [5(6)-methyl-*as*-triazinyl]) urea, 1-(4-nitrophenyl)-3-[3-(5,6-dimethyl-*as*-triazinyl)] urea and 1-(4 nitrophenyl)-3-[3 - (5,6,7,8-tetrahydro-1,2,4-benzotriazinyl)] urea. Such compounds are effective against coccidiosis in poultry when administered in the diet at concentration of about 0.025 to 0.1%.

The following examples directed to the preparation of some representative 3-amino-*as*-triazines are presented to illustrate specific embodiments, and the general applicability, of this invention.

EXAMPLE 1

Production of 3-amino-*as*-triazine

A solution of aminoguanidine was prepared by adding 200 gm. of aminoguanidine bicarbonate to 310 ml. of 6 *N* hydrochloric acid followed by 100 ml. of 4 *N* sodium hydroxide. To this mildly basic solution was added simultaneously 300 gm. of 30% aqueous glyoxal and 400 ml. of 4 *N* sodium hydroxide at such a rate as to retain the temperature below about 50°C. and the pH at about 8 to 10. A crystalline product deposited in a few minutes. After standing for about 30 minutes the reaction mixture was chilled to 0°C. and 3-amino-*as*-triazine was recovered by filtration. The product was washed with cold saturated sodium chloride and dried. It was recrystallized from water and then ethanol to give a product in the form of greenish, refractive needles melting at 177—179°C. The ultraviolet absorption spectrum had maxima in 0.1 N HCl at 2310 Å and in 0.1 *N* NaOH at 2250 Å and 3220 Å.

EXAMPLE 2

Production of 3-amino-5(6)-methyl-*as*-triazine

To a slightly basic aqueous solution containing 108 gm. of aminoguanidine was added 223 gm. of 44.3% aqueous methylglyoxal. At the same time 250 ml. of 4 *N* sodium hydroxide was added at such a rate as to maintain a pH of about 8—10 and a temperature below 50°C. After stirring for 20 minutes the reaction mixture was allowed to stand for an hour during which time 3-amino-5(6)-methyl-*as*-triazine deposited as pale yellow crystals. The reaction mixture was cooled to 0°C., solid potassium hydroxide added and the product collected by filtration. It was washed with ice-water and ethanol. After recrystallization from ethanol it had a melting point of 181—183°C.

EXAMPLE 3

Production of 3-amino-5,6-dimethyl-*as*-triazine

To 330 ml. of 2.5 *N* hydrochloric acid was added 100 gm. of aminoguanidine bicarbonate and then 250 ml. of 2.5 *N* sodium hydroxide. To this solution was added 63.4

gm. of 2,3-butanedione. After the temperature reached 45°C. 110 ml. of 2.5 *N* sodium hydroxide was added. The reaction mixture was allowed to stand 45 minutes, then chilled to 0°C., and the precipitated 3-amino-5,6-dimethyl-*as*-triazine collected by filtration. After recrystallization from water it had a melting point of 210—211°C. The ultraviolet absorption spectrum showed inflections at 2200 Å and 2950 Å in 0.1 *N* HCl, maxima at 2260 Å and 3175 Å in pH 7 buffer, and maxima at 2270 Å and 3150 Å in 0.1 *N* NaOH.

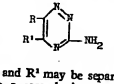
EXAMPLE 4

Production of 3-amino-5,6,7,8-tetrahydro-1,2,4-benzotriazine

To 250 ml. of 2.5-*N* hydrochloric acid was added 85 gm. of aminoguanidine bicarbonate and then 23 ml. of 2.5 *N* sodium hydroxide. To the clear solution was added with stirring 69.7 gms. of cyclohexenedione-1,2, in 60 ml. of ethanol. At the same time 210 ml. of additional 2.5 *N* sodium hydroxide was added to maintain a uniform basic pH of about 8—10. The reaction mixture was allowed to stand for 15 minutes, chilled to 0°C., and the precipitated 3-amino - 5,6,7,8-tetrahydro-1,2,4-benzotriazine collected by filtration and air dried. After recrystallization from water the product melted at 204—206°C.

What we claim is:—

1. 3 - Amino - *as* - triazines having the formula:



in which R and R^1 may be separate or joined to complete a second ring, each of R and R^1, when separate, representing a hydrogen atom or hydroxy or alkyl group, and R and R^1, when joined, representing a polymethylene or substituted polymethylene radical.

2. 3-Amino-*as*-triazine.

3. 3-Amino - 5(6)-methyl-*as*-triazine, obtainable by the reaction of methylglyoxal with aminoguanidine.

4. 3-Amino-5,6-dimethyl-*as*-triazine.

5. 3 - Amino - 5,6,7,8-tetrahydro - 1,2,4-benzotriazine.

6. 3-Amino-5-hydroxy-*as*-triazine.

7. 3-Amino - 5 - hydroxy - 6 - methyl-*as*-triazine.

8. The process for producing a 3-amino-*as*-triazine of the formula set forth in Claim 1, which comprises reacting aminoguanidine or one of its salts with a 1,2-dicarbonyl compound of the formula:

where R and R^1 are as defined in Claim 1.

9. A process according to Claim 8, wherein the dicarbonyl reactant is glyoxal or a monoalkyl glyoxal.

10. The process for producing 3-amino-5(6) - methyl - *as* - triazine which comprises reacting methylglyoxal with amino guanidine.

11. The process of producing 3-amino-5,6-dimethyl-*as*-triazine which comprises reacting 2,3-butanedione with aminoguanidine.

12. The process of producing 3-amino-5,6,7,8-tetrahydro-1,2,4-benzotriazine which comprises reacting cyclohexanedione-1,2 with aminoguanidine.

13. A process for producing a compound having the formula of Claim 1, substantially as hereinbefore described, with particular reference to the foregoing examples.

14. A compound according to Claim 1, whenever prepared by a method as claimed in any one of Claims 8—13.

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